PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Patent of

Nobutaka TANI et al.

U.S. Patent No.: 4,637,994

Issue Date: January 20, 1987

For: ADSORBENT AND PROCESS FOR PREPARING THE SAME

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Your Applicant, Kanegafuchi Kagaku Kogyo Kabushiki Kaisha, a corporation organized and existing under the laws of Japan, represents that it is the Assignee of the entire interest in and to United Letters Patent No. 4,673,994 granted to Nobutaka Tani and Tsuneo Hayashi on January 20, 1987 for ADSORBENT AND PROCESS FOR PREPARING THE SAME by virtue of an Assignment in favor of Kanegafuchi Kagaku Kogyo Kabushiki Kaisha recorded by the United States Patent and Trademark Office. Your Applicant, acting through its duly authorized representative, hereby submits this application for extension of patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. 1.710 et seq.). For convenience, the information contained in this application will be

presented in the format following the requirements of 37 C.F.R. 1.740.

1. 37 C.F.R. § 1.740(a)(1) - The approved product is known as the Liposorber LA-15® System ("LA-15 System"). The LA-15 System, a Class III medical device, is a low density lipoprotein apheresis system.

2. 37 C.F.R. § 1.740(a)(2) - The U.S. Food and Drug Administration ("FDA") performed the required regulatory review of the LA-15 System pursuant to the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 301 et seq. The specific provision of the Federal Food, Drug and Cosmetic Act governing the premarket approval process for Class III medical devices is 21 U.S.C. § 360e.

3. 37 C.F.R. § 1.740(a)(3) - The FDA granted Kaneka America Corporation ("KAC"), a wholly-owned U.S. subsidiary of Kanegafuchi Kagaku Kogyo Kabushiki Kaisha, final approval for commercial marketing of the LA-15 System on February 21, 1996. A copy of the FDA's final approval letter for the LA-15 System is attached to this application as Exhibit 1.

4. 37 C.F.R. § 1.740(a)(5) - Kanegafuchi Kagaku Kogyo Kabushiki Kaisha is submitting this application for extension of patent term within the sixty day period permitted for

submission of such application pursuant to 37 C.F.R. § 1.720(f). The last day on which this application may be submitted is April 22, 1996.

5. 37 C.F.R. § 1.740(a)(6) - By this application Kanegafuchi Kagaku Kogyo Kabushiki Kaisha seeks extension of the following patent:

Patent Number - 4,637,994

Inventors - Nokutaka Tani and
Tsuneo Hayashi

Date of Issue - January 20, 1987

Date of Expiration - December 1, 2003

During prosecution of U.S. Patent 4,637,994, a Terminal Disclaimer was submitted disclaiming the portion of the term of U.S. Patent 4,637,994 subsequent to the expiration date of U.S. Patent 4,576,928. A copy of this Terminal Disclaimer is attached to this application as Exhibit 2. The Terminal Disclaimer Exhibit 2 does not recite a date certain after which the term of U.S. Patent 4,637,994 is disclaimed, but disclaims the portion of its term which would fall subsequent to the expiration of U.S. Patent 4,576,928.

U.S. Patent 4,576,928 was filed on December 1, 1983, and was granted March 18, 1986. In accordance with the Uraguay Round Agreements Act (URAA), the term of U.S. Patent 4,576,928, since it was in force on date of enactment of the

URAA, shall be the greater of a 20-year term as provided under 35 U.S.C. § 154(a) or 17 years from grant, subject to any Terminal Disclaimers. 35 U.S.C. § 154(c)(1) Patent term extensions under 35 U.S.C. § 156 are calculated from the 20-year term from filing date for such a patent, if that term is longer than the 17-year from grant patent term. Merck and Co. v. Kessler, 36 USPQ 2d. 1727 (E.D. Va., 1995).

6. 37 C.F.R. § 1.740(a)(7) - A copy of the patent for which Kanegafuchi Kagaku Kogyo Kabushiki Kaisha hereby seeks an extension of patent term is attached to this application as Exhibit 3.

7. 37 C.F.R. § 1.704(a)(8) - No disclaimer other than the above-noted Terminal Disclaimer (Exhibit 2), certificate of correction, or reexamination certificate has been issued with respect to U.S. Patent 4,637,994. Two maintenance fee payments have been made for U.S. Patent 4,637,994. Attached hereto as Exhibit 4 are:

(a) Duplicate maintenance fee statement from U.S. Patent and Trademark Office stating that the first maintenance fee payment was paid.

(b) Duplicate maintenance fee statement from the U.S. Patent and Trademark Office stating that the second maintenance fee payment has been paid.

8. 37 C.F.R. § 1.704(a)(9) - U.S. Patent 4,637,994 claims the approved product or a method of using or manufacturing the approved product. Set forth below is each applicable patent claim and a description of the manner in which each such applicable patent claim reads on the approved product or method of using or manufacturing the approved product.

Claim 1

1. An adsorbent for removing low and/or very low density lipoprotein from body fluid in extracorporeal circulation treatment, which comprises a water-insoluble porous hard gel with exclusion limit of 10^6 to 10^9 daltons on which a sulfated compound is immobilized by a covalent linkage; said sulfated compound being a compound obtained by sulfation of a hydroxy-containing compound.

The approved product is the liposorber LA-15® system ("LA-15 System"). The LA-15 System is a low density lipoprotein apheresis system. The LA-15 System is an integrated system that includes:

1. Sulflux® FS-05 plasma separator.
2. Liposorber® LA-15 LDL (low density lipoprotein) Adsorption Column.
3. Tubing system for plasmapheresis.
4. Apheresis unit.

The Liposorber® LA-15 LDL Adsorption Column reads on claim 1 of U.S. Patent 4,637,994 because:

(a) The Liposorber® LA-15 LDL Adsorption Column contains an adsorbent which adsorbs and eliminates low density lipoprotein (LDL) from plasma of a patient perfused through the device in an extracorporeal circulation treatment, utilizing the entire LA-15 System. The adsorbent is a dextran sulfate-cellulose in which dextran sulfate is a ligand immobilized on the surface of microporous cellulose beads via covalent bonding. The microporous cellulose beads are a water-insoluble microporous hard gel having an exclusion limit within the range of 10^6 to 10^8 daltons. The dextran sulfate which is immobilized by a covalent linkage on the gel is prepared by sulfation of a hydroxy-containing compound.

(b) From the above, the Liposorber® LA-15 LDL adsorbent meets and reads on all limitations of the adsorbent claimed by claim 1 of U.S. Patent 4,637,994.

Claim 2

2. The adsorbent of claim 1, wherein said water-insoluble porous hard gel is a water-insoluble porous polymer hard gel.

The cellulose gel used in the Liposorber® LA-15 LDL adsorption column is a water-insoluble porous polymer hard gel.

Claim 3

3. The adsorbent of claim 2, wherein said water-insoluble porous polymer hard gel is a porous cellulose gel.

The cellulose gel used as the adsorbent in the Liposorber® LA-15 LDL adsorption column is a porous cellulose gel.

Claim 6

6. The adsorbent of claim 1, wherein the sulfated compound is a sulfated carbohydrate.

The dextran sulfate which is the sulfated compound of the adsorbent of the Liposorber® LA-15 LDL Adsorption Column is a sulfated carbohydrate.

Claim 7

7. The adsorbent of claim 6, wherein the sulfated carbohydrate is a sulfated saccharide.

The dextran sulfate used in the adsorbent of the Liposorber® LA-15 LDL Adsorption Column is a sulfated saccharide.

Claim 8

8. The adsorbent of claim 7, wherein the sulfated saccharide is a sulfated polysaccharide.

The dextran sulfate used as the sulfated compound in the Liposorber® LA-15 LDL Adsorption Column is a sulfated polysaccharide.

Claim 9

9. The adsorbent of claim 8, wherein the sulfated polysaccharide is a member selected from the group consisting of heparin, dextran sulfate, chondroitin sulfate and salts thereof.

The sulfated compound used in the adsorbent of the Liposorber® LA-15 LDL Adsorption Column is dextran sulfate; thus, it is one of the members of the grouping of claim 9.

Claim 10

10. The adsorbent of claim 9, wherein the dextran sulfate, a salt thereof or a mixture of the dextran sulfate

and the salt has an intrinsic viscosity of not more than 0.12 dl/g and a sulfer (sic) content of not less than 15% by weight.

The dextran sulfate used in the adsorbent of the Liposorber® LA-15 LDL Adsorption Column has an intrinsic viscosity of 0.02 to 0.04 dl/g and a sulfur content within the range of 15 to 20 percent by weight, thereby reading on the terms of claim 10 describing dextran sulfate having an intrinsic viscosity of not more than 0.12 dl/g and a sulfur content of not less than 15 percent by weight.

Claim 11

11. The adsorbent of claim 1, wherein the sulfated compound is a sulfated polyhydric alcohol.

Dextran sulfate, which is the sulfated compound used in the adsorbent of the Liposorber® LA-15 LDL Adsorption Column, is a sulfated polyhydric alcohol.

Claim 12

12. The adsorbent of claim 1, wherein the exclusion limit is 10^6 to 10^8 daltons.

The adsorbent used in the Liposorber® LA-15 LDL Adsorption Column has an exclusion limit of 10^6 to 10^8 daltons.

Claim 13

13. The adsorbent of claim 1, wherein said sulfated compound is immobilized in an amount of 0.02 to 100 mg/ml of bed volume.

The dextran sulfate used in the adsorbent of the Liposorber® LA-15 LDL Adsorption Column is immobilized on the cellulose gel in an amount between 1.5 mg/ml and 4.0 mg/ml of bed volume, thereby falling within the range of immobilization amount of 0.02 to 100 mg/ml of bed volume of claim 13.

Claim 14

The adsorbent of claim 13, wherein the sulfated compound is immobilized in an amount of not less than 0.2 mg/ml of bed volume.

Since the dextran sulfate is immobilized in an amount of between 1.5 and 4.0 mg/ml of bed volume, it is present in an amount not less than 0.2 mg/ml of bed volume.

Claim 15

15. A process of preparing an adsorbent for removing low and/or very low density lipoprotein from body fluid in extracorporeal circulation treatment comprising a water-insoluble porous hard gel with exclusion limit of 10^6 to 10^9 daltons in which a sulfated compound is immobilized , wherein said water-insoluble porous hard gel is reacted with epichlorhydrin or a polyoxirane compound to introduce epoxy groups on to the gel, and then the resulting epoxy-activated gel is reacted with the sulfated compound; said sulfated compound being a compound obtained by sulfation of a hydroxy-containing compound.

Claim 15 sets forth a process for manufacturing the adsorbent used in the Liposorber® LA-15 LDL Adsorption Column. In addition to describing the column in accordance with the characteristics of claim 1 (which characteristics have been treated above with respect to claim 1), claim 15 adds process terminology stating that the water-insoluble porous hard gel is reacted with epichlorhydrin or a polyoxirane compound to introduce the epoxy groups onto the gel, and then the resulting epoxy-activated gel is reacted with the sulfated compound. In the process of preparing the adsorbent for the Liposorber® LA-15 LDL Adsorption Column, the cellulose gel, which is a water-insoluble porous hard gel having an exclusion limit of 10^6 to 10^8 daltons, is reacted with epichlorhydrin to

introduce epoxy groups on to the gel, and the resultant epoxy-activated gel is reacted with dextran sulfate as the sulfated compound.

Claim 16

The process of claim 15, wherein said water-insoluble hard gel is a water-insoluble porous polymer hard gel.

The cellulose gel used in the Liposorber® LA-15 LDL Adsorption Column is a water-insoluble porous polymer hard gel.

Claim 17

The process of claim 16, wherein said water-insoluble porous polymer hard gel is a porous cellulose gel.

The cellulose gel used as the adsorbent in the Liposorber® LA-15 LDL Adsorption Column is a porous cellulose gel.

Claim 18

18. The process of claim 15, wherein said sulfated compound is dextran sulfate, a salt thereof or a mixture of the dextran sulfate and the salt; said dextran sulfate, the salt thereof or the mixture of the dextran sulfate and the

salt being reacted with the epoxy-activated gel in a concentration of not less than 3% by weight based on the weight of the whole reaction system excluding the dry weight of the porous hard gel.

In the preparation of the adsorbent used in the Liposorber® LA-15 LDL Adsorption Column, dextran sulfate as the sulfated compound is reacted with the epoxy-activated cellulose gel in a concentration of 20 to 30 percent by weight based on the weight of the whole reaction system excluding the dry weight of the cellulose gel, thereby being used in a concentration of not less than 3 percent by weight based on the weight of the whole reaction system excluding the dry weight of the porous hard gel as set forth in claim 18.

Claim 19

19. The process of claim 18, wherein the porous hard gel is a porous cellulose gel.

The cellulose gel used as the adsorbent in the Liposorber® LA-15 LDL Adsorption Column is a porous cellulose gel.

9. 37 § 1.740(a)(10)(v) - In connection with the LA-15 System, Kanegafuchi Kagaku Kogyo Kabushiki Kaisha, through KAC, submitted two applications for investigational device exemption ("IDE") and two applications for premarket approval ("PMA"). The FDA approved KAC's LA-40 IDE (IDE number G850224) on April 18, 1986 and conditionally approved KAC's LA-15 IDE (IDE number G880069) on October 21, 1988. An LA-40 premarket approval application was submitted on March 24, 1988 (PMA number P880019) and an LA-15 premarket approval application was submitted on March 26, 1991 (PMA number P910018). The FDA approved KAC's LA-15 PMA on February 21, 1996.

The first clinical investigation under the LA-40 IDE was begun on July 10, 1986. The first clinical investigation under the LA-15 IDE was begun on December 22, 1988. (See Exhibits 5 and 6.)

10. 37 C.F.R. § 1.740(a)(11) - A brief description of the activities undertaken by Applicant and KAC during the applicable regulatory review period is attached hereto as Exhibit 7. Exhibit 7 is inclusive of a chronology of the major communications with the FDA from November 29, 1985 to February 21, 1996. Further, from the time of first human clinical trial with the LA-15 System (December 22, 1988) until receipt of the FDA approval letter (February 21, 1996) and thereafter, the LA-15 System has continually been used in human clinicals.

11. 37 C.F.R. § 1.740(a)(12) - Kanegafuchi Kagaku Kogyo Kabushiki Kaisha believes that Patent No. 4,637,994 is eligible for extension pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.720. In accordance with 35 U.S.C. § 156(g)(3) and 37 C.F.R. § 1.777, Kanegafuchi Kagaku Kogyo Kabushiki Kaisha believes that this patent should be extended for five years. Because Patent No. 4,637,994 was issued after September 24, 1984, five years is the maximum permissible patent term extension under the applicable statue and regulations. See 35 U.S.C. § 156(g)(6)(A); 37 C.F.R. § 1.777(d)(5).

U.S. Patent 4,637,994 satisfies all the requirements for an extension as follows:

(a) 35 U.S.C. § 156(a)

U.S. Patent 4,637,994 claims a product and a method of manufacturing a product which is a medical device, or a system of a medical device approved by the FDA.

(b) 35 U.S.C. § 156(a)(1)

The term of U.S. Patent 4,637,994 has not expired before submission of this application.

(c) 35 U.S.C. § 156(a)(2)

The term of U.S. Patent 4,637,994 has never been extended.

(d) 35 U.S.C. § 156(a)(3)

This application for extension is submitted by the owner of record of U.S. Patent 4,637,994 in accordance with the requirements of 35 U.S.C. § 156(d) and the rules of the U.S. Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4)

The approved medical device, the LA-15 System, has been subjected to a regulatory review period before the commercial marketing or use thereof.

(f) 35 U.S.C. § 156(a)(5)(A)

The commercial marketing or use of the product, the Liposorber® LA-15 LDL Adsorption Column of the LA-15 System, after the regulatory review period is the first permitted commercial marketing or use of the product under the applicable provision of the Federal Food, Drug and Cosmetic Act under which said regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4)

No other patent has been extended for the same regulatory review period for the product, the Liposorber® LA-15 LDL Adsorption Column of the LA-15 System.

The length of extension of the patent term of U.S. Patent 4,637,994 claimed by Applicant is five (5) years. The length

of the extension was determined pursuant to 37 C.F.R. § 1.777 as follows:

Hereinbelow, the length of extension for U.S. Patent 4,637,994 is calculated in three ways, depending upon whether the regulatory review time period involving the LA-40 device is to be included and if so, whether the LA-40 or LA-15 PMA date is used. Applicant's opinion is that the regulatory review time period involving the LA-40 device (including the LA-40 PMA date) should be used in calculating the length of patent term extension.

The LA-40 device is a LDL (low density lipoprotein) adsorption column containing an adsorbent identical to that found in the adsorption columns of the approved LA-15 System. Plasma is separated from the patient's blood by suitable means not part of the LA-40 device, the plasma is passed through the LA-40 device for adsorption of LDL by the device; and then the plasma is returned to the patient by suitable means not part of the LA-40 device. Therefore, the LA-40 device corresponds to and contains the same adsorbent as found in the Liposorber® LA-15 Adsorption Column of the LA-15 System, without the presence of the other components (the plasma separator, the tubing system for plasmaphereses and the apheresis unit) of the LA-15 System. Accordingly, within the meaning of 37 C.F.R. § 1.710, 37 C.F.R. § 1.777 and 35 U.S.C. § 156, the patent claimed approved product, which is the adsorbent of the

Liposorber® LA-15 LDL Adsorption Column, and which is used in combination with other components to form the LA-15 System approved device, is the same as the adsorbent found in the LA-40 adsorption column.

11A. Calculation of length of patent term extension including regulatory review period of the LA-40 device and LA-40 PMA date.

(a)(1) The number of days in the period beginning on the date a clinical investigation on humans involving the device was begun (7/10/86 for LA-40 device) and ending on the date an application was initially submitted under section 515 (3/24/88 for LA-40 device) - a total of 624 days.

(a)(2) And the number of days in the period beginning on the date the application was initially submitted under section 515 (3/24/88 for the LA-40 device) and ending on the date said application was approved under such act (2/21/96 for the LA-15 System) - a total of 2,890 days.

Under 37 C.F.C. § 1.777(d), the following subtractions are made from the above calculated regulatory review period:

(d)(1)(i) Number of days on and before the date on which the patent issued, which is 195 days

(d)(1)(ii) Number of days determined by the secretary of HHS during which Applicant did not act with due diligence, which is zero days

(d)(1)(iii) One-half the days remaining in the above period (a)(1) after that period is

reduced in accordance with (d)(1)(i) and (ii), which is 214 days, leaving a total of 3,105 days in the regulatory review period.

11B. Calculation of length of patent term extension including the regulatory review of the LA-40 device and the LA-15 PMA date.

(b)(1) The number of days in the period beginning on the date a clinical investigation on humans involving the device was begun (7/10/86 for LA-40 device) and ending on the date an application was initially submitted under section 515 (3/26/91 for LA-15 System) - a total of 1,721 days.

(b)(2) And the number of days in the period beginning on the date the application was initially submitted under § 515 (3/26/91 for the LA-15 System) and ending on the date said application was approved under such act (2/21/96 for the LA-15 system) - a total of 1,793 days.

Under 37 C.F.C. § 1.777(d), the following subtractions are made from the above calculated regulatory review period:

(d)(1)(i) Number of days on and before the date on which the patent issued, which is 195 days

(d)(1)(ii) Number of days determined by the secretary of HHS during which Applicant did not act with due diligence, which is zero days

(d)(1)(iii) One-half the days remaining in the above period (b)(1) after that period is

reduced in accordance with (d)(1)(i) and (ii), which is 763 days, leaving a total of 2,556 days in the regulatory review period.

11C. Calculation of length of patent term extension based on regulatory review period beginning with the first human trial involving the LA-15 system and LA-15 PMA date..

(c)(1) The number of days in the period beginning on the date a clinical investigation on humans involving the device was begun (12/22/88 for LA-15 system) and ending on the date an application was initially submitted under section 515 (3/26/91 for LA-15 System) - a total of 825 days.

(c)(2) And the number of days in the period beginning on the date the application was initially submitted under section 515 (3/26/91 for LA-15 System) and ending on the date such application was approved under such act (2/21/96 for LA-15 System) - a total of 1,793 days.

Under 37 C.F.C. § 1.777(d), the following subtractions are made from the above calculated regulatory review period:

(d)(1)(i) Number of days on and before the date on which the patent issued, which is zero days

(d)(1)(ii) Number of days determined by the secretary of HHS during which Applicant did not act with due diligence, which is zero days

(d)(1)(iii) One-half the days remaining in the above period (c)(1) after that period is

reduced in accordance with (d)(1)(i) and (ii), which is 412 days, leaving a total of 2,206 days in the regulatory review period.

Under 37 C.F.R. § 1.777 (d)(2) and (3), the number of days determined in 11A (3,105 days), 11B (2,556 days) and 11C (2,206 days) extends the original term of US4637994 as shortened by any Terminal Disclaimer (December 1, 2003) to a time beyond 5 years from the expiration date of the patent (since such 5 years is equal to 1,826 days) but less than 14 years from FDA Approval (February 21, 2010). Accordingly, US4637994, which was granted on January 20, 1987 is subject to the five (5) year term extension limitation of 37 C.F.R. § 1.777 (d)(5).

12. 37 C.F.R. § 1.740(13) - Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought (see § 1.765).

13. 37 C.F.R. § 1.740(a)(14) - In accordance with 37 C.F.R. § 1.20(j), Applicant is submitting the required filing fee of $1,060 along with this application.

14. 37 C.F.R. § 1.740(a)(15) - Inquires and correspondence regarding this application may be directed to Applicant's legal counsel in this matter, as follows:

Louis Gubinsky
SUGHRUE, MION, ZINN, MACPEAK & SEAS
2100 Pennsylvania Avenue, N.W.
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(202) 293-7060

15. 37 C.F.R. § 1.740(a)(16) - A duplicate of this application (including all papers filed therewith) is enclosed and certified as such.

16. 37 C.F.R. § 1.740(a)(17) - An oath or declaration pursuant to 37 C.F.R. § 1.740(b) is enclosed herewith.

Respectfully submitted,

Louis Gubinsky
Registration No. 24,835

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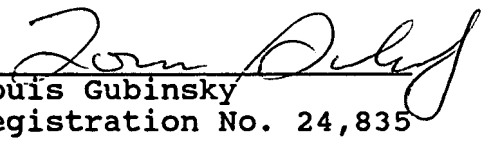
Date: April 18, 1996

CERTIFICATION

The undersigned hereby certifies that this Application for Extension of Patent Term under 35 U.S.C. § 156, including its exhibits and supporting papers and attachments, is being submitted as one original along with a duplicate copy thereof.

Respectfully submitted,



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Date: April 18, 1996